Risk factors for idiopathic orbital inflammation: a case-control study

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Risk factors for idiopathic orbital inflammation: a case—control study

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ABSTRACT

Objective To identify risk factors involved in the development of idiopathic orbital inflammation (IOI).

Methods Case—control study of 69 adults who had had a first episode of IOI and 296 adult controls with rhegmatogenous retinal detachment (RD) selected from three orbital centres in The Netherlands between 2000 and 2006. Participants filled out a questionnaire on demographic factors, medical history, health status and exposures for the 2 years prior to disease presentation. In addition, women were questioned about previous or current pregnancies and their hormonal status. ORs and accompanying 95% CIs for IOI in relation to potential risk factors such as body mass index (BMI), bisphosphonates and autoimmune disease were estimated. ORs were adjusted for age, sex, socio-economic status, smoking and blunt orbital trauma using logistic regression. Analyses were carried out both with and without multiple imputation of missing values.

Results The risk of IOI was increased in participants who had a higher BMI (third vs first tertile: OR, 2.88; 95% CI 1.32 to 6.32) and in participants who used bisphosphonates (OR 8.68; 95% CI 1.16 to 65.0). The risk was decreased in participants with a higher socioeconomic status (third vs first tertile: OR 0.38; 95% CI 0.17 to 0.84) and in women who were older at first childbirth (third vs first tertile: OR 0.14; 95% CI 0.03 to 0.64). An almost significant association was found for IOI and autoimmune disease (OR 2.56; 95% CI 0.93 to 7.05).

Conclusions IOI is associated with lower socioeconomic status, higher BMI and use of oral bisphosphonates. In women, IOI is also associated with younger age at first childbirth.

INTRODUCTION

Idiopathic orbital inflammation (IOI) is among the most frequent orbital diseases encountered by ophthalmologists.1 IOI is a non-infectious inflammation of the orbital soft tissues for which no cause is found after local and systemic evaluation.2 The term IOI refers to a collection of different entities, including idiopathic sclerosing orbital inflammation,3 idiopathic granulomatous orbital inflammation,4 dacrocyoadenitis5 and orbital myositis,6 which makes patients with IOI an inhomogeneous patient population.

IOI presents with various signs and symptoms of inflammation, most frequently pain, eyeball motility disturbances and proptosis.2 Due to the orbital soft tissue swelling, IOI may mimic a neoplasm (‘orbital pseudotumour’ is the historical term for IOI). The clinical course of IOI ranges from mild and self-limiting to devastating orbital sclerosis with blindness.2

IOI, as is indicated by the word ‘idiopathic’ in the disease name, is of unknown aetiology. Many case reports and series have highlighted possible etiological factors for IOI, including autoimmune diseases7 and medications such as bisphosphonates,8 lithium9 and chemotherapeutics.10 Retroperitoneal fibrosis is a systemic disease entity that is similar in many respects to IOI.11 Ergot derivatives,12 13 asbestos14 and a genetic predisposition15 have been reported as risk factors for retroperitoneal fibrosis.

To our knowledge, systematic research of the risk factors for IOI has not been previously conducted. In this case—control study, we explore associations between a number of risk factors and IOI.

METHODS

This study was designed as a case—control study. Our patients came from three orbital clinics in The Netherlands between 2000 and 2006. Patients with IOI were identified by searching the hospital diagnosis database for ICD-9 code 376.1. ICD-9 code 376.0, which was primarily used for orbital infection, was excluded.

Patient records were reviewed, and patients with all of the following three criteria were included in the study: (1) a clinical picture of orbital inflammation with either no improvement after antibiotic therapy and prompt improvement after systemic prednisone, or non-specific inflammation after an orbital tissue biopsy; (2) no local or systemic identifiable cause of the inflammation; and (3) age 18 or older and residing in The Netherlands. For example, sarcoidosis, lupus and Wegener granulomatosis were excluded as causes of IOI. Only patients who had had a first episode of IOI were included in the study. The localisation of IOI was determined by reviewing radiology images and was categorised as localised myositis, localised dacryoadenitis or diffuse inflammation. Histology reports, when available, were reviewed and classified as classic, sclerosing or granulomatous inflammation.7 Laterality and corticosteroid treatment were recorded.

For the controls, adults who had had a first episode of a rhegmatogenous retinal detachment (RD) were identified using the hospital surgical database. For each patient with IOI, we randomly selected four controls who had been diagnosed as having RD in the same hospital and in the same year and month as the patient. Hospital-based controls were chosen for availability, similar geographic area, high response rate and similar recollection of information. These controls were
Characteristics of responders and non-responders among patients and controls

Table 1 Characteristics of responders and non-responders among patients and controls

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th></th>
<th></th>
<th>Controls</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Responders (n = 69)</td>
<td>Non-responders (n = 34)</td>
<td>p Value*</td>
<td>Responders (n = 295)</td>
<td>Non-responders (n = 115)</td>
<td>p Value*</td>
</tr>
<tr>
<td>Mean (SD) age (years)</td>
<td>52.6 (13.4)</td>
<td>49.0 (14.6)</td>
<td>0.224</td>
<td>59.6 (11.8)</td>
<td>60.7 (15.6)</td>
<td>0.465</td>
</tr>
<tr>
<td>Male sex</td>
<td>29 (42%)</td>
<td>13 (38%)</td>
<td>0.332</td>
<td>190 (64%)</td>
<td>73 (64%)</td>
<td>0.909</td>
</tr>
<tr>
<td>Orbital clinic</td>
<td>0.116</td>
<td></td>
<td></td>
<td>0.204</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>12 (17%)</td>
<td>8 (24%)</td>
<td></td>
<td>53 (18%)</td>
<td>26 (23%)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>24 (35%)</td>
<td>17 (50%)</td>
<td></td>
<td>125 (42%)</td>
<td>38 (33%)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>33 (48%)</td>
<td>9 (26%)</td>
<td></td>
<td>117 (40%)</td>
<td>51 (44%)</td>
<td></td>
</tr>
<tr>
<td>Years of diagnosis</td>
<td>0.676</td>
<td></td>
<td></td>
<td>0.005</td>
<td></td>
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</tr>
<tr>
<td>2000–2001</td>
<td>8 (12%)</td>
<td>3 (9%)</td>
<td></td>
<td>30 (10%)</td>
<td>14 (12%)</td>
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</tr>
<tr>
<td>2002–2003</td>
<td>16 (23%)</td>
<td>7 (21%)</td>
<td></td>
<td>54 (18%)</td>
<td>38 (33%)</td>
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</tr>
<tr>
<td>2004–2005</td>
<td>23 (33%)</td>
<td>9 (26%)</td>
<td></td>
<td>102 (35%)</td>
<td>26 (23%)</td>
<td></td>
</tr>
<tr>
<td>2006–2007</td>
<td>22 (32%)</td>
<td>15 (44%)</td>
<td></td>
<td>109 (37%)</td>
<td>37 (32%)</td>
<td></td>
</tr>
</tbody>
</table>

*p Values calculated by χ² test.
adjusted the effect of other potential risk factors for the confounding effect of age (continuous variable), sex and socio-economic status (tertiles). In addition, we adjusted for pack years (tertiles) of smoking and for blunt trauma to the orbit.

The risk of IOI was lower for those with higher socio-economic status (third vs first tertile: adjusted OR, 0.36; 95% CI 0.16 to 0.81). The risk increased with higher BMI (third vs first tertile: adjusted OR 2.88; 95% CI 1.52 to 5.62). Use of bisphosphonates was associated with IOI (adjusted OR 8.68; 95% CI 1.16 to 65.0) with imprecision due to low absolute numbers of bisphosphonate users. The association between bisphosphonate use and IOI persisted in the stratum of postmenopausal females (adjusted OR 9.29; 95% CI 1.98 to 72.0), after additional adjustment for female hormone supplements (adjusted OR 9.55; 95% CI 1.21 to 72.5). A trend for association between IOI and autoimmune disease was found, although it was not statistically significant (adjusted OR 2.56; 95% CI 0.93 to 7.05).

Female patients were more often premenopausal at diagnosis than female controls, but this association disappeared after adjustment for age, socio-economic status, smoking and trauma (adjusted OR 1.07; 95% CI 0.22 to 5.19). For women who had given birth, a higher age at first childbirth was associated with a lower risk of IOI (third vs first tertile: adjusted OR 0.15; 95% CI 0.08 to 0.72). The other variables in table 1 did not show a clear relationship with IOI. Little seasonal variation of IOI presentation was found, with 26% presenting in winter, 22% in spring, 25% in summer and 28% in autumn.

Multiple imputation changed the association measures on average by 16.5% to a weaker association in 25 variables and a stronger association in 12 variables (table 2).

**COMMENT**

In this study, risk factors for the development of IOI are evaluated by comparing patients with IOI to controls with RD. We found a significant association between IOI and sex (female), age (younger), socio-economic status (lower), BMI (higher), use of bisphosphonates and age at birth of first child (younger). The association between autoimmune disease and IOI was almost statistically significant.

In the IOI group, there were relatively more females (61%) than in the RD group (39%), and the patients with IOI were, on average, 7 years younger than the controls with RD (mean age 53 and 60 years, respectively). These differences highlight the different demographic features of IOI and RD, where RD is associated with male sex and older age.

We used the highest level of education of the patient and of their partner as a surrogate variable for socio-economic status. RD has been associated with a lower education level (education beyond age 16 years: OR 0.6; 95% CI 0.3 to 1.1). This association may be explained by ocular trauma as a cause of RD (10% in a large survey of RD; it was 6% in our study), and a higher risk of ocular trauma in craftsmen. However, in our study, we found lower educational levels to be associated with IOI as well, even after adjusting for ocular trauma.

As is known from clinical practice, a higher BMI was associated with IOI. The BMI was calculated from height and weight at diagnosis of IOI and, therefore, should not have been affected by the use of corticosteroids. The relation between metabolic regulation and the immune system has been of interest in recent research. Obesity is associated with a chronic inflammatory response. In obesity, the inflammatory response appears to be triggered and reside predominantly in adipose tissue. The high orbital fat content in obese patients may explain why inflammatory diseases occur in the orbit. Leptin is thought to be central to the link between obesity and autoimmunity because leptin is secreted by adipocytes and can trigger the production of proinflammatory and pathogenic cytokines.

The cases of three patients who developed IOI after administration of intravenous bisphosphonates have been reported. The proposed mechanism of action is the release of the inflammatory cytokines IL-1 and IL-6 triggered by bisphosphonates. The prevalence of bisphosphonate use in the population is low (it was 2.3% in our study). Therefore, the association between bisphosphonate use and IOI will not have major clinical consequences.

We decided to look at the role of female hormones in IOI because of the intimate relationship between hormones and the immune system. Oestrogens are implicated as enhancers of humoral immunity, and androgens and progesterone are natural immune suppressors. We looked for higher oestrogen levels in patients with IOI, which is suggested by a small female preduction and higher age at menopause. However, the observation of a lower number of pregnancies in patients with IOI, when oestrogens are high, does not support an aetiological role of high oestrogens in IOI. The statistically significant association between the lower age at first childbirth and IOI suggests that female hormones play a role in IOI, but it is not clear how this relates to oestrogens and progesterone. Lower age at first childbirth may also be a risk indicator of risk factor clustering, as occurs with breast cancer.

An association between IOI and autoimmune diseases was postulated by Mombaerts and Koornneef, who found that 10% of patients with IOI had a concurrent autoimmune disease. We found concurrent autoimmune diseases in 12% of patients with IOI (OR 2.56; 95% CI 0.93 to 7.05). Although the association was not statistically significant, it is suggestive of an autoimmune pathogenesis in IOIA genetic predisposition, or a disregulated immune system with autoantibodies against multiple self-antigens could explain the high co-occurrence of IOI with autoimmune diseases.

Of the proposed possible risk factors, we did not find an association between IOI and ergot derivatives, lithium, LSD, chemotherapy, asbestos, trauma or family history. The equal number of days patients with IOI and controls with RD had flu or colds suggests that they had similar immune system functioning.

A case–control study is implicitly limited in that only associations can be described, but no causality inferred. The quality of such a study is highly dependent on the selection of controls. In this study, it is not possible to draw conclusions about common risk factors between IOI and RD. Because RD is caused by posterior vitreous detachment, we thought RD unlikely to be associated with risk factors other than age, sex and ocular trauma. We did not use a control group of healthy volunteers because we expected an unacceptable low response rate. A cohort design was considered inefficient because of the long inclusion time of 7 years.

By selecting all patients with IOI (some who were not histologically confirmed), we have selected a heterogeneous group of diseases. This will likely dilute associations of risk factors that are specific for subgroups like dacryoadenitis and myositis. However, the sample size is too low for subgroup analysis. Limiting the study to histologically confirmed patients would have introduced a selection bias and would have yielded a lower number of cases.

Recall bias due to the retrospective nature of this study was considered to have influenced both patients and controls in equal amounts. The effect of missing values was evaluated by using
Table 2  Risk factors for patients with idiopathic orbital inflammation and controls with retinal detachment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n=69)</th>
<th>Controls (n=295)</th>
<th>Adjusted OR*</th>
<th>Adjusted, multiple imputed OR*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N observed</td>
<td>Percentage</td>
<td>p Value†</td>
<td>OR 95% CI</td>
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<tr>
<td><strong>Demographics</strong></td>
<td></td>
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<tr>
<td>Male sex</td>
<td>28</td>
<td>40.6</td>
<td>0.001</td>
<td>0.33</td>
</tr>
<tr>
<td>Age (years) at diagnosis</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>21—54</td>
<td>35</td>
<td>50.7</td>
<td></td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>55—64</td>
<td>24</td>
<td>34.8</td>
<td></td>
<td>0.54</td>
</tr>
<tr>
<td>65—88</td>
<td>10</td>
<td>14.5</td>
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<td>0.20</td>
</tr>
<tr>
<td><strong>Socio-economic status‡</strong></td>
<td></td>
<td></td>
<td>0.091</td>
<td></td>
</tr>
<tr>
<td>Tertile 1</td>
<td>22</td>
<td>31.9</td>
<td></td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Tertile 2</td>
<td>25</td>
<td>36.2</td>
<td></td>
<td>0.87</td>
</tr>
<tr>
<td>Tertile 3</td>
<td>22</td>
<td>31.9</td>
<td></td>
<td>0.36</td>
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<tr>
<td><strong>Body mass index§</strong></td>
<td></td>
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<td>0.090</td>
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<tr>
<td>Tertile 1</td>
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<td>24.6</td>
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<td>1.00 (Reference)</td>
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<tr>
<td>Tertile 2</td>
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<td>31.9</td>
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<td>1.86</td>
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<td>Tertile 3</td>
<td>30</td>
<td>43.5</td>
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<tr>
<td><strong>Exposures</strong></td>
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</tr>
<tr>
<td>Smoking§</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>23</td>
<td>34.3</td>
<td></td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Former</td>
<td>25</td>
<td>37.3</td>
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<td>1.59</td>
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<tr>
<td>Current</td>
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<tr>
<td>Pack years of cigarette smoking</td>
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<tr>
<td>0</td>
<td>23</td>
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<tr>
<td>1—15</td>
<td>16</td>
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<td>1.67</td>
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<td>16—110</td>
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<td><strong>Medication use</strong></td>
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<td>8.68</td>
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<td>Ergot derivatives</td>
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<td>1.5</td>
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<td>1.65</td>
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<tr>
<td>Lithium</td>
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<td>0.0</td>
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<tr>
<td>Chemotherapy</td>
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<td>1.5</td>
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<tr>
<td>Thyroid hormones</td>
<td>2</td>
<td>2.9</td>
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<td><strong>Environmental exposure</strong></td>
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<td>Asbestos (any)</td>
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<td>10.3</td>
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<td>LSD</td>
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<td>0.0</td>
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<td>1.000</td>
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<td>Physical or emotional distress</td>
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<td>27.5</td>
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<td><strong>Health status</strong></td>
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</tr>
<tr>
<td>Past medical history</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoimmune disease</td>
<td>8</td>
<td>12.3</td>
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<tr>
<td>Diabetes</td>
<td>5</td>
<td>7.7</td>
<td></td>
<td>0.814</td>
</tr>
<tr>
<td>Blunt trauma to orbit</td>
<td>2</td>
<td>2.9</td>
<td></td>
<td>0.547</td>
</tr>
<tr>
<td>Surgery of orbit, sinuses or facial bones</td>
<td>2</td>
<td>2.9</td>
<td>4</td>
<td>1.4</td>
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<td><strong>Family history (first—third-degree relatives)</strong></td>
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<td>Orbital inflammatory disease</td>
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<td>3.6</td>
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<td>1.000</td>
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<td>Lupus</td>
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<td>5.4</td>
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<td>Thyroiditis</td>
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<td>12.5</td>
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<td>0.280</td>
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<td>Myasthenia</td>
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<td>3.6</td>
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<td>Uveitis</td>
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<td>0.0</td>
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<td>0.607</td>
</tr>
<tr>
<td>Diabetes</td>
<td>29</td>
<td>51.8</td>
<td></td>
<td>0.291</td>
</tr>
<tr>
<td>Flu or cold days per year</td>
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<td>0.984</td>
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</tr>
<tr>
<td>0—4</td>
<td>25</td>
<td>40.3</td>
<td></td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>5—8</td>
<td>18</td>
<td>29.0</td>
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<td>0.95</td>
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<tr>
<td>9—200</td>
<td>19</td>
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<td><strong>For women</strong></td>
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<td>0.235</td>
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</tr>
<tr>
<td>Pregnancies (no)</td>
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<td>6</td>
<td></td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>1—2</td>
<td>24</td>
<td>58.5</td>
<td></td>
<td>0.93</td>
</tr>
<tr>
<td>3—12</td>
<td>11</td>
<td>26.8</td>
<td></td>
<td>0.44</td>
</tr>
<tr>
<td>Female hormone supplement</td>
<td>13</td>
<td>33.3</td>
<td></td>
<td>0.121</td>
</tr>
</tbody>
</table>

Continued
multiple imputation. Multiple imputations caused the associations to attenuate in a majority of variables. A group of variables that was largely affected by multiple imputations were variables measured only on females, which is probably due to the lower number of observations. Multiple imputations did not alter the conclusions but might have resulted in more valid and precise effect estimates.16

In conclusion, this study describes the first systematic search for risk factors for IOI. Novel and statistically significant associations with IOI are found between lower socio-economic status, higher BMI, use of oral bisphosphonates and a lower age at first childbirth in women. An important and almost statistically significant association has been found between autoimmune diseases and IOI.

**Table 2 Continued**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n=69) N observed</th>
<th>Controls (n=295) N observed</th>
<th>p Value†</th>
<th>Adjusted OR*</th>
<th>OR 95% CI</th>
<th>Adjusted, multiple imputed OR*</th>
<th>OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenopausal</td>
<td>24</td>
<td>92</td>
<td>&lt;0.001</td>
<td>1.07</td>
<td>0.22 to 5.19</td>
<td>0.92</td>
<td>0.22 to 3.88</td>
</tr>
<tr>
<td>For postmenopausal women</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Age (years) at menopause</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27–45</td>
<td>4</td>
<td>29</td>
<td>40.3</td>
<td>1.00</td>
<td>(Reference)</td>
<td>1.00</td>
<td>(Reference)</td>
</tr>
<tr>
<td>47–51</td>
<td>10</td>
<td>25</td>
<td>34.7</td>
<td>4.85</td>
<td>0.94 to 24.9</td>
<td>3.15</td>
<td>0.79 to 12.5</td>
</tr>
<tr>
<td>52–58</td>
<td>7</td>
<td>18</td>
<td>25.0</td>
<td>3.35</td>
<td>0.69 to 16.8</td>
<td>2.12</td>
<td>0.49 to 9.11</td>
</tr>
<tr>
<td>For women with children</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years) at birth first child</td>
<td>0.141</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14–24</td>
<td>26</td>
<td>49</td>
<td>46.2</td>
<td>1.00</td>
<td>(Reference)</td>
<td>1.00</td>
<td>(Reference)</td>
</tr>
<tr>
<td>25–27</td>
<td>9</td>
<td>28</td>
<td>26.4</td>
<td>0.79</td>
<td>0.23 to 2.71</td>
<td>0.72</td>
<td>0.24 to 2.23</td>
</tr>
<tr>
<td>28–36</td>
<td>6</td>
<td>14</td>
<td>27.4</td>
<td>0.15</td>
<td>0.03 to 0.72</td>
<td>0.26</td>
<td>0.07 to 0.96</td>
</tr>
</tbody>
</table>

*Adjusted for gender, age (continuous), social economic status, packyears of smoking and blunt trauma to the orbit; however, gender, age, social economic status, packyears and blunt trauma to the orbit are adjusted for four of five variables.
†p Values calculated using the χ² test.
‡Tertile 1 Educationage 16 years, Tertile 2 Education age 17–18 years, Tertile 3 Education>age 18 years.
§Tertile 1 body mass index<23.7, Tertile 2 23.7<body mass index<26.6, Tertile 3 body mass index≥26.6.
¶Smoking is not adjusted for packyears because of a high correlation between the variables.

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Br J Ophthalmol 2011 95: 360-364 originally published online July 31, 2010
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